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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/374,213	08/13/1999	DAVID STERN	59472/JPW/SH	3469

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EXAMINER	
WEGERT, SANDRA L	
ART UNIT	PAPER NUMBER
1647	11

DATE MAILED: 04/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/374,213	Applicant(s) STERN ET AL.	
	Examiner Sandra Wegert	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26 and 34-58* is/are pending in the application.

4a) Of the above claim(s) *1-26,34-40,42,43,45 and 47-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41,44,46 and 55-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments, and/or Claims

The amendment filed 23 January 2002 (Paper No. 10) has been entered. Claims 30-33 were cancelled by the Applicant. Claims 1-26, 34-40, 42, 43, 45 and 47-54 were withdrawn by the examiner.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 41, 44, 46, 55, 56, 57 and 58 are currently under examination.

Withdrawn Objections and/or Rejections

Claims

The objection to Claim 30 as recited in the previous Office Action (5 July, 2001; p. 3) for depending from a cancelled claim is withdrawn in that Claim 30 has been cancelled (Paper 10, 23 January 2002).

35 USC § 103, Obviousness.

The rejection of claims 41, 44, 46, 55 and 56 under 35 U.S.C. 103(a) as recited in the previous Office Action (5 July, 2001; p. 3-5), is withdrawn in light of the explanations by Applicant and the new 35 U.S.C. 103(a) rejection, as discussed below.

Maintained Rejections/Objections

Figures

The objections to the Figures as recited in the previous office action (5 July 2001; p. 3)- is maintained. Applicants have indicated that they will submit formal drawings in the event there are allowable claims.

Claims

The objections to Claims 45 and 55 because they recite or encompass non-elected inventions - as recited in the previous Office Action (5 July 2001; p. 3)- is maintained.

35 USC § 112, First paragraph.

Note: The listing of references in the specification is not a proper Information Disclosure Statement, and is therefore not of record. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper."

The rejection of claims 41, 44, 46 and 55-56 under 35 U.S.C. 112 as recited in the previous Office Action (5 July, 2001; p. 5-7), is *maintained.* The Specification discloses using the soluble form of the receptor to inhibit binding of amyloid to *RAGE* in PC12 cells transfected with *RAGE.* The disclosure also describes using the methods of the Invention to inhibit binding of amyloid to splenic cells of mice, as measured by changes in NFκB, for example. The Examiner stressed that there is no link described in the disclosure that would enable the methods of treating a *Subject* or disease *in vivo* as applicable to humans.

The Applicants' arguments primarily center on "common denominators of fibrillar pathologies" (Specification, page 80, for example). Applicant has argued that use of s*RAGE* to block peripheral amyloidosis in a mouse model is an example of an enabling in vivo use (Paper 10, 23 January 2002, p. 16). Applicant also argued that accumulation of amyloid in the spleens of mice, the association of increased amyloid with IL-6 production (p 21), and its blockade by administration of sRAGE in a dose-dependent manner, are evidence that the methods described in the instant Specification can be applied to the increased amyloidosis associated with Alzheimer's disease. A paper by Schenck, et al (1999, Nature, 400: 173) similarly stresses treatments aimed at reducing amyloid in a transgenic model of Alzheimer's disease. The Picciotto, et al paper (1998, Physio. Rev. 78: 1131) was submitted by the Applicant to support the argument that mice models of Alzheimer's disease are relevant and enabling for the claimed Invention. Finally, Applicants point to studies that administered cyclo-oxygenase inhibitors to mice and humans as presumed evidence of the similarity between Alzheimer's disease and the transgenic mouse model of amyloidosis (Weggen, et al, 2001, Nature 414: 212) and

discuss evidence from the instant Specification that administration of sRAGE dose-dependently suppressed splenic amyloid burden (p. 21).

Applicant's arguments (Paper 10, 23 January 2002) have been fully considered but are not deemed to be persuasive for the following reasons:

In support of their arguments that mice models of AD are relevant and enabling for the methods of the Instant Application, Applicants submitted the papers by Hsaio, et al and Picciotto, et al. Hsaio's group produced transgenic mice which appear to produce abnormally high β-amyloid. Picciotto, et al discuss that there are now several transgenic strains of mice demonstrating increased amyloid burden. The brains of the transgenic mice in Hsaio's paper and several other studies have demonstrated plaques. The amyloid over-producing transgenic mice of Hsaio's group showed a delayed syndrome of impaired learning and cerebral plaques (p. 99). Applicants submit that these mouse models adequately represent a human model of amyloidosis, namely Alzheimer's disease, and by implication, can be used as a model of treatment of Alzheimer's disease using the methods of the current invention.

Applicants also point to the commentary by Hardy (1997, PNAS, 94: 2095) which discusses amyloid deposition as involved or causative of diseases ranging from faulty egg laying in nematodes to Alzheimer's disease and Down syndrome in humans.

However, there exist several problems with using mouse models of Alzheimer's disease in which there are defects in amyloid processing to predict whether a therapy in humans will be effective. As the Hsaio study points out (p. 99), Alzheimer's disease is a

disease of unknown etiology, and cognitive deficits do not necessarily correlate well with amyloid deposition (first paragraph). Additionally, tests of learning and memory in animals cannot be seen to reflect the cognitive deficits seen in humans with Alzheimer's disease. The experiments cited by the Applicant utilize a simple maze to test the animals' memory, or a swimming test. Many factors can contribute to the results obtained from such studies: sedation, reduction of motivation (e.g., satiety), or motor impairments, to name a few. Importantly, "higher" motor functions, such as use of language and associative learning, are compromised early in the etiology of AD and in fact, are the defining deficits in the disease (Pearlman, et al, eds, Neurobiology of Disease, p. 311). Such deficits that distinguish Alzheimer's diseases from other amyloid diseases or from more localized causes of cerebral damage (i.e, stroke) cannot be adequately evaluated by means of an animal model.

Finally, it should be noted that the papers submitted with the Applicants' response are silent as to the possible contribution of the *AGE* receptor to both the pathogenesis of animal amyloidosis and Alzheimer's disease, thus poorly predictive of a method of treatment involving *RAGE* or *sRAGE*.

Similarly, the rejection of claims 57 and 58 under 35 U.S.C. 112 as recited in the previous Office Action (5 July, 2001; p. 5-7), is maintained. The claims read on using s*RAGE* to inhibit binding of ligand and thus modulate a disease state involving β-sheet fibrils. The Specification discloses using the soluble form of the receptor to inhibit binding of amyloid to *RAGE* in PC12 cells transfected with *RAGE*. The disclosure also

describes using the methods of the Invention to inhibit binding of amyloid to splenic cells of mice, as measured by changes in NFκB, for example. The Examiner argued that there is no nexus described in the disclosure that would enable the methods of the Invention as applied to Alzheimer's disease or to inhibiting binding of ligand to *RAGE* in a diseased subject. The Examiner stressed the complexity of Alzheimer's disease, and the involvement, for example, of many types of proteins in plaque formation, besides β-amyloid.

The Applicant has argued that use of s*RAGE* to specifically block amyloid formation in vitro, as well as the fact that one could use in vitro data together with in vivo data in the literature, as a whole demonstrate the ability of the disclosed invention to modulate a disease state. The applicant argues that the specification discloses "common denominators of fibrillar pathologies" (Specification, page 80). However, no data is referred to in the Specification or in the literature that demonstrates the processes described and claimed as pertaining to Alzheimer's disease, or to use in *subjects*, for example. Importantly, there is no evidence presented of the chain of events that presumably links amyloid to Alzheimer's disease *by means of* RAGE. In addition, using the methods of the Invention to inhibit binding of amyloid to transfected cells or splenic cells of mice, as measured by changes in NFκB, for example, is not shown to be further linked to preventing a disease process.

New Rejections

35 USC § 103(a), Obviousness.

Claims 41, 44, 46 and 55-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyata, et al (1996, J. Clin. Invest., 98: 1088) in view of Yan, et al (1997, PNAS, 94: 5296). As alluded to by the Applicant (5 July 2001, p. 6), it is possible that *cell-type* or location may be important in distinguishing the Invention of the Instant Application from similar methods in the receptor field. Evidence of prior art should therefore reflect the type of cell used for the relevant experiments as well as the methods.

The Instant Specification discloses using the soluble form of the receptor to inhibit binding of amyloid to *RAGE* in PC12 cells transfected with *RAGE* or in splenic cells or mononuclear phagocytes. The disclosure also describes using the methods of the Invention to inhibit binding of amyloid to splenic cells of mice, as measured by changes in NFκB, for example.

Miyata, et al discuss the presence of RAGE in mononuclear phagocytes (Miyata, et al, 1996, J. Clin. Invest., 98:1088). They state that this may be significant because the AGE ligand AGE-β_2M (amyloid), by interacting with RAGE on mononuclear phagocytes, may contribute to the damage of peripheral tissues in long-term hemodialysis patients. They demonstrated specific binding of AGE ligand to MPs, dose-dependent

transduction processes, and inhibition of AGE ligand binding using a specific antibody to RAGE (see, Fig. 1). Miyata, et al, did not measure oxidative damage directly after exposure of RAGE-containing cells to ligand. They did, however, measure cell chemotaxis, and in fact, blocked that process using the soluble form of the RAGE receptor. They did provide a strong indication that cellular damage could be triggered by RAGE ligand, in their use of N-acetylcysteine to inhibit indicators of oxidative stress (Figure 4).

Yan, et al teaches binding of a β-sheet fibril, namely Amyloid-β, to the *RAGE* receptor on microglia. They further measure the resultant oxidative stress reaction triggered by activation of *RAGE* on those cells. Measurements of oxidative stress included measurement of inflammatory pathways involving transcription factor NF-κ-B. They suggest that these processes may contribute to the cellular pathologies seen in Alzheimer's disease. They do not teach inhibition of binding of β-sheet fibril to *RAGE*.

Since Yan, et al did not teach inhibition of this binding event- nor especially inhibition using a soluble receptor, and since Miyata's group did not teach evidence of oxidative damage- the teachings of Miyata, et al and Yan, et al were combined to render the instant Invention obvious. As binding of a ligand to *RAGE* triggers a cascade of events leading to oxidative damage (e.g., Yan, et al), and because Miyata, et al use soluble receptors to compete for ligand binding, it would be obvious to someone skilled in the art to use *sRAGE* in the manner described in the Instant Application to inhibit ligand binding.

Conclusion:

Claims 41, 44, 46, 55, 56, 57 and 58 are rejected for the reasons cited above.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (703) 308-9346. The examiner can normally be reached Monday - Friday from 9:30 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SLW

4/06/02

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